Dietary intake is associated with the prevalence of uterine leiomyoma in Korean women: A retrospective cohort study

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Abstract

Objective: To evaluate the association between dietary intake and the prevalence of uterine leiomyoma (UL) in Korean women.

Design: A retrospective cross-sectional study with dietary intake assessment.

Setting: A Health check-up center

Population: A cohort of 672 Korean women aged 25–65 years from a previous study.

Methods: Dietary intake was assessed using food frequency questionnaire (FFQ), and the presence of UL was evaluated by ultrasonography. Multiple logistic regression models were used to analyze the relationship between dietary intake and the prevalence of UL with adjustment for confounding factors.

Main Outcome Measures: Dietary intake and prevalence of UL.

Results: A total of 219 (32.6%) women were diagnosed with UL. High intakes of fish and poultry were associated with a high prevalence of UL; ORs (95% CIs) comparing top vs. bottom quartiles were 1.70 (1.02-2.84; p trend = 0.049) for fish intake and 1.85 (1.09-3.14; p trend = 0.07) for poultry intake. High intake of dairy products was inversely associated with the prevalence of UL (OR 0.59, 95% CI 0.36–0.98; p trend = 0.06).

When we examined pre- and post-menopausal women separately, the association for poultry intake was generally limited to postmenopausal women. In premenopausal women, those with higher vegetable intake had a lower prevalence of UL (OR 0.47, 95% CI 0.22 -1.01 for top vs. bottom quartiles; p trend = 0.01).

Conclusions: We found that high intakes of fish and poultry, but low intake of dairy products, were associated with a higher prevalence of UL. Vegetable intake was inversely associated with the prevalence of UL in premenopausal women.

1 Introduction

Uterine leiomyoma (UL) is the most common benign gynecologic tumor, affecting approximately 25% of women of reproductive age, with peak prevalence occurring at age 50 and a lifetime risk of up to 70%.¹⁻³

While the pathophysiological mechanisms underlying the development of ULs at the cellular and molecular level have not been fully elucidated, they appear to be sex-hormone (estrogen and progesterone) dependent diseases, typically appearing after menarche, growing during reproductive ages, and regressing along with declining reproductive hormone levels after menopause. ⁴⁻⁷ Other known associated factors include age, ethnicity (with 2-3 times higher incidence in blacks than in other races), genetics, number of pregnancies (more common in women who have had fewer pregnancies or deliveries), obesity, lack of physical exercise, and some dietary factors. ⁸, ⁹

As data on the relationship between dietary factors and malignant diseases such as breast or endometrial cancer, which are presumed to be estrogen dependent, have been reported mostly in terms of the potential of chemoprevention and long-term prognosis,¹⁰⁻¹³, the role of dietary nutrition as a factor that can be modified
in the development and growth of UL has become a topic of interest, as dietary intake may alter either endocrine function or molecular biologic milieu.\textsuperscript{14}

According to previous studies, dietary patterns or some nutrients have shown significant associations with ULs. While the consumption of fruits and vegetables has shown a protective effect against ULs, findings have been inconsistent for other foods such as dairy, meat, or fish.\textsuperscript{8, 15-17} Meanwhile, studies that have reported the association between nutritional intake analysis and the prevalence of UL in Korean women are limited. This study aimed to investigate the association between dietary intake and prevalence of UL stratified by menopausal status among Korean women.

2 Materials and Methods

2.1 Study design and participants

This study retrospectively used a prospectively collected cohort from our previous study.\textsuperscript{18} Participants who underwent health checkups, including colonoscopy and dietary intake assessment, using a semi-quantitative food-frequency questionnaire (FFQ) at the Seoul National University Hospital Gangnam Center in Seoul, Korea, between May and December 2011, were registered. Among them, only women participants who also had pelvic ultrasonography during the study period were enrolled. Individuals who had already undergone hysterectomy or who did not take the pelvic ultrasound examination were excluded. A total of 672 women were finally included in this study.

Postmenopausal status was defined as the absence of menstruation for at least 1 year. Women in perimenopausal status (irregular cycles of more than 7\textsuperscript{th} days differences or missed two or more cycles of menstruation within 12 months) were classified as premenopausal women.\textsuperscript{19}

2.2 Clinical and laboratory assessment

Baseline characteristics, such as medication use (e.g., antidiabetic, antihypertensive, or lipid-lowering agents), underlying diseases (diabetes, hypertension, and dyslipidemia), smoking history, amount of physical activity, alcohol consumption, and reproductive characteristics (age at menarche, parity, age at first delivery, and menopausal status) were recorded during a medical interview using a structured questionnaire before a routine gynecologic examination. Anthropometric parameters (body mass index (BMI), waist circumference (WC), and blood pressure (BP)), and biochemical results (fasting plasma glucose, triglycerides, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein (HDL)-cholesterol) were retrospectively reviewed for each individual, as previously described.

2.3 Assessment of uterine leiomyoma

ULs were assessed through ultrasound examination using GE LOGIQ\textsuperscript{®}9 (GE healthcare, General Electric Co., UK) equipment. The examination was performed by one of the three gynecologists who were obstetrics and gynecology specialists (M-J Kim, JJ Kim, and S Kim) with more than eight years of experience. The presence of UL was assessed only by intracavitary (mostly transvaginal, some transrectal) pelvic ultrasound examination, and cases with UL were defined as having one or more nodules of typical leiomyoma with \textsuperscript{\textless}10mm in length.

2.4 Assessment of Dietary intake

Dietary intake data were assessed prior to the examination on the same day using a validated 106-item Food Frequency Questionnaire (FFQ),\textsuperscript{21} with assistance from a registered dietician. Participants reported their usual frequency of consumption of various foods and typical portion sizes for the year preceding the interview date. Each food item had 9 options for frequency (ranging from “never or less than once per month” to “3 times per day”) and three options for portion size (“small”, “medium”, or “large”). Fruit and vegetable intake included all raw, cooked, canned, frozen or dried forms of fruits and most edible vegetables. For the analysis, we examined the food consumption and total energy intake. Only items corresponding to the ten categories (vegetables/fruit, vegetables, fruits, red meat, processed meat (grouped into tertiles, two
categories in postmenopausal women), poultry, fish, dairy product, milk, and alcohol (grouped into tertiles) were included in the analyses and the amount of food intake was divided into quartiles.

2.5 Assessment of risk factors

Metabolic syndrome (MetS) was defined according to the harmonized definition proposed by the International Diabetes Federation/American Heart Association/National Heart, Lung, and Blood Institute. A patient was diagnosed with MetS if they met three or more of the following criteria: abdominal obesity (waist circumference [?]85 cm for Korean women as proposed by the Korean Society for the Study of Obesity), high triglycerides (TG) ([?]150 mg/dL), low HDL-cholesterol (< 50 mg/dL), high fasting glucose([?]100 mg/dL) or treatment for diabetes, and increased blood pressure ([?]130/85 mmHg) or treatment for hypertension.

Current smokers were defined as those who had been smoking at least one cigarette per day during the previous 12 months, while past-smokers were considered those who discontinued smoking for at least 12 months before inclusion in the study. “Ever smokers” refers to respondents who are current or past smokers.

Physical activity (PA) was measured by the modified Korean version of the PA questionnaire from the National Health and Nutrition Examination Survey. PA was quantified using metabolic equivalent (MET)-minutes per week.

2.6 Statistical analysis

Numerical variables were expressed as mean+-standard deviation, and categorical variables were presented as numbers and percentages. If the parameters were not normally distributed, log_{10} transformation was used for analysis. The relationship between each dietary intake and UL was evaluated using binary logistic regression analyses. As ULs usually shrink after menopause due to a drastic drop in serum estrogen levels, the data were analyzed separately for two groups based on their menopausal status (premenopausal, including peri-menopausal, vs. postmenopausal). The median value of each tertile or quartile was included in the models as a continuous variable for trend testing. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the associations using multiple logistic regression models. In Model 1, we adjusted for confounding variables including age (years, continuous), BMI (kg/m^2, <18.5, 18.5–23, 23–25, 25[?]), total energy intake (kcal/d, quintile), and LDL-cholesterol (mg/dL, continuous). In Model 2, we further adjusted for all clinically relevant parameters, including menopausal status (premenopausal vs. postmenopausal), age at menarche (years old, [?]11, 11<), age at first delivery combined with parity (nulliparity, years old, <25, 25[?]), alcohol intake (g/d, continuous), smoking status (never, or ever) and physical activity (MET-min/week, tertile). All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). We used 2-sided statistical tests, and p -values less than 0.05 were considered statistically significant.

3 Results

A total of 672 women were included in the study, with 383 (57%) being premenopausal and the age range being 25–65 years old (mean age 50.1 years). Of these, 219 (32.6%) were diagnosed with UL, with no significant difference in prevalence between pre- and postmenopausal women (34.5% vs. 30.1%, respectively; p = 0.23). Compared to women without UL, those with UL were older (51.0 +- 7.4 vs. 49.7 +- 9.5 years, p = 0.01), had a higher BMI (22.4 +- 3.2 vs. 21.9 +- 2.8 kg/ m^2, p = 0.03), and higher LDL-cholesterol levels (128.2 +- 31.3 vs. 122.3 +- 32.4 mg/dL, p = 0.01). There were no significant differences in terms of reproductive, lifestyle, comorbidities, or laboratory parameters between the two groups (Table 1).

Table 2 shows the associations between dietary intake and the prevalence of UL in all participants, as analyzed through age-adjusted and two-stage multiple logistic regression models. Among all participants, higher fish intake showed an increased association with the prevalence of UL (Q4 vs. Q1: OR_2 1.70, 95 % CI 1.02-2.84; ptrend = 0.049). Higher poultry intake in Q2 and Q4 was associated with an increased prevalence of UL compared to Q1 (Q2 vs. Q1: OR_2 1.81, 95% CI 1.05-3.12; Q4 vs. Q1: OR_2 1.85, 95% CI 1.09-3.14), although the dose-response trend was not statistically significant (p for trend = 0.07).

On the other hand, higher intake of dairy products in Q3 and Q4 exhibited a significant inverse association
with the prevalence of UL compared to Q1 (Q3 vs. Q1: OR\textsubscript{2} 0.59, 95% CI 0.36-0.96; Q4 vs. Q1: OR\textsubscript{2} 0.59, 95% CI 0.36-0.98), but the dose-response relationship was not statistically significant (\(p\)\text{trend} = 0.06). The Q3 intake of milk showed a significant inverse association compared to Q1 (Q3 vs. Q1: OR\textsubscript{2} 0.56, 95% CI 0.36-0.87).

A subgroup analysis was conducted for pre- and postmenopausal women (Table 3, Figure 1). In premenopausal women, vegetable intake was significantly inversely association with the UL prevalence in a dose-dependent manner (\(p\)\text{trend} = 0.01), although no single quartile intake of vegetables reached statistical significance compared with the lowest quartile (Q4 vs. Q1: OR\textsubscript{2} 0.47, 95% CI 0.22-1.01). Intake of red meat (Q2 vs. Q1: OR\textsubscript{2} 0.47, 95% CI 0.24-0.91) and dairy products (Q3 vs. Q1: OR\textsubscript{2} 0.46, 95% CI 0.23-0.93) showed an inverse association with UL prevalence. The intake of fish was significantly association with increased prevalence of UL (Q3 vs. Q1: OR\textsubscript{2} 2.83, 95% CI 1.38-5.78).

In postmenopausal women, higher fish intake was significantly associated with higher UL prevalence (\(p\)\text{trend} = 0.02), although no statistically significant association was demonstrated in each quartile group. Intake of processed meat (top vs. bottom: OR\textsubscript{2} 2.33, 95% CI 1.21-4.49) and poultry (Q2 vs. Q1: OR\textsubscript{2} 2.17, 95% CI 1.04-4.51) showed a significant association with an increased UL prevalence.

4. Discussion

4.1 Main findings

The principal findings of our study were as follows:

1) Among all participants, 219 (32.6%) were diagnosed with UL: 132 out of 383 (34.5%) pre-menopausal women and 87 out of 289 (30.1%) postmenopausal women, with no statistically significant differences in the prevalence of UL between pre- and postmenopausal women (\(p = 0.23\)).

2) High intakes of fish and poultry were associated with a high prevalence of UL; ORs (95% CIs) comparing top vs. bottom quartiles were 1.70 (1.02-2.84; \(p\)\text{trend} = 0.049) for fish intake and 1.85 (1.09 -3.14; \(p\)\text{trend} = 0.07) for poultry intake. However, high intake of dairy products was inversely associated with the prevalence of UL (OR 0.59, 95% CI 0.36–0.98; \(p\)\text{trend} = 0.06).

3) When we examined pre- and post-menopausal women separately, we found a similar increased prevalence with fish intake and decreased prevalence with dairy product intake. However, the association for poultry intake was generally limited to postmenopausal women. In premenopausal women, those with higher vegetable intake had a lower prevalence of UL (OR 0.47, 95% CI 0.22 -1.01 for top vs. bottom quartiles; \(p\)\text{trend} = 0.01).

4.2 Strengths and limitations

This is the first Korean study to investigate the association between dietary factors and UL, and a validated Food Frequency Questionnaire (FFQ) was used, which has good reproducibility and validity. All UL cases and non-cases were diagnosed by pelvic ultrasound examination, which is the most sensitive and clinically useful diagnostic tool for UL. Additionally, dietary intake information was evaluated synchronously with clinical factors, and the association was analyzed with consideration for menopausal status and other relevant confounding factors.

However, this study has several limitations. Firstly, there may be unavoidable information errors in the data acquired through self-reported food intake questionnaires. Secondly, the cross-sectional nature of the study limits the interpretation of causal inferences, and it is possible that people who are already diagnosed with UL may have had such a dietary pattern. Moreover, this study could be biased towards individuals with medium to high socioeconomic status who voluntarily paid US $500–1300 for their private health check-up and who tend to be more interested in their health and more motivated to engage in a healthier lifestyle. Thirdly, as a single-center study, this population cannot be assumed to represent all Korean women. Fourthly, this study could not examine the influence of nutrients from foods on dietary intake analyses. Data on the concentration of their metabolites, blood markers of inflammation, reproductive or growth hormones, which are presumed
to mediate these associations, were not available for this study. Lastly, this study excluded women without an intact uterus who may have undergone hysterectomy due to UL-related symptoms. Therefore, severe or symptomatic cases have been inevitably excluded.

4.3 Interpretations

In our study, the prevalence of UL was found to be 33%. Although there was no statistically significant difference, premenopausal women showed a slightly higher prevalence of UL than postmenopausal women (35% vs. 30%). About 50% of ULs are asymptomatic and can be accurately diagnosed with ultrasound.1, 23 In our study, ULs were diagnosed using strict criteria, and as a result, ULs were confirmed in about one-third of the total population, which is similar to the results from a previous Korean study where ULs were observed in 37.5% of the population diagnosed through pelvic ultrasonography during health check-ups, regardless of the presence or absence of symptoms.24

We observed a significant association between fish consumption and a high prevalence of UL in premenopausal women (Q3 vs. Q1: OR2 2.83, 95% CI 1.38-5.78) and a significant dose-dependent association in postmenopausal women (Q4 vs. Q1: OR2 2.09, 95% CI 0.96-4.57; p trend = 0.02). However, an Italian case-control study reported an inverse association,25 and no difference was found in Chinese and Japanese studies.26, 27 In a study on US black women, small increases in risk associated with intakes of long-chain omega-3 fatty acids were the most consistent associations of fat intake with UL.28 A cohort study in the US showed that the prevalence of UL was 1.2 times higher in women who consumed sport fish from the Great Lakes for 10 years, supporting the possibility that polychlorinated biphenyls (PCBs) exposures from fish consumption may increase the risk of UL.29 Most studies so far have analyzed fish consumption in terms of dietary fat, and the relationship between dietary fat and UL is largely conflicting.15 In a recent prospective study including 1,171 premenopausal African-American women in the US, intakes of total fat and saturated, monounsaturated, polyunsaturated, and trans-fat were not appreciably associated with UL incidence, but the intake of the marine ω-3 polyunsaturated fatty acid, docosahexaenoic acid, was associated with a 49% higher UL incidence (Q4 vs. Q1: HR 1.49, 95% CI 1.04, 2.14, p trend = 0.01). As the authors pointed out, it is still unclear whether these associations are derived from the nutritional components of fish or by the possible accumulation of endocrine disrupting persistent organic pollutants such as PCBs.30

In this study, vegetable intake showed a significant protective association with the prevalence of UL in premenopausal women. The odds of the highest quartile of vegetable intake over the bottom quartile were 0.47 (95% CI 0.22–1.01), and the overall dose-dependent relationship was statistically significant (p trend = 0.01). These results are in good agreement with previous studies. For example, in the Black Women’s Health Study, women who had four or more servings of fruits or vegetables per day had a significantly lower risk of developing UL (IRR = 0.90, 95% CI 0.82–0.98).31 In a case-control study including 273 women, of whom 94% were of Han Chinese ethnicity, vegetable and fruit intake showed an inverse correlation with UL (OR 0.5, 95% CI 0.3–0.9) in premenopausal women.26 Moreover, other studies have shown that women with UL consumed green vegetables and fruits less frequently than women without UL.25, 32 These protective associations are presumed to be caused by mechanisms such as decreased bioavailable estrogen and growth factors,33, 34 or by increased levels of phytochemicals that have anti-inflammatory activities.35, 36 However, the protective effect of fruit consumption was not observed in this study: the odds for vegetable and fruit intake, and fruit intake alone were 0.62 (95% CI 0.31–1.25) and 0.72 (95% CI 0.37–1.41) for the highest quartile over the lowest quartile, respectively. This is consistent with a case-control study on 843 Italian women, which showed that vegetables were more protective than fruits regarding UL prevalence (OR 0.5, 95% CI 0.4–0.6 for green vegetables, OR 0.8, 95% CI 0.6–1.0 for fruit consumption).25

We found a protective association between dairy consumption and UL prevalence (Q4 vs. Q1: OR2 0.59, 95% CI 0.36-0.98 for all participants, Q3 vs. Q1: OR2 0.46, 95% CI 0.23-0.93 for premenopausal women). Similarly, one study reported a protective effect of frequent consumption of milk and low-fat dairy products against UL occurrence, with no association found for butter, cheese, and ice cream, and a weak protective effect observed for yogurt consumption among African American women.37 However, an Italian study found no association between milk and cheese intake and UL risk.25 A Chinese prospective cohort study even found
an increased risk when milk and soymilk were analyzed together. Dairy products are a complex group of foods containing various nutritional components, including calcium, vitamin D, phosphorus, butyric acid, among others. Moreover, the composition of dairy products varies according to different regions around the globe, making it challenging to evaluate their association with disease risk. In a large prospective cohort study spanning over 18 years, no clear associations were observed between overall dairy consumption and UL risk. However, the study found that the intake of yogurt and dietary calcium was associated with a reduced risk of UL development.

In terms of the association between meat consumption and UL, we observed a protective association with some levels of red meat intake in premenopausal women (Q2 vs. Q1: OR0.47, 95% CI 0.24-0.91). On the other hand, we found an increased association between processed meat (higher vs. lower: OR2.33, 95% CI 1.21-4.49) and poultry (Q2 vs. Q1: OR2.17, 95% CI 1.04-4.51) consumption and UL prevalence in postmenopausal women. A case–control study conducted on Italian women showed that significant consumption of meats such as beef or ham was associated with an increased risk of UL, while the risk was insignificant in the Chinese population. We categorized meat into red meat, processed meat, and poultry. The intake of processed meat and poultry showed an association with increased UL prevalence only in postmenopausal women, while the intake of red meat revealed a lower prevalence of UL only in premenopausal women. There is a limitation in interpreting these associations as the absolute amount of meat intake in this population is relatively low. However, it seems that processed meat, rather than red meat, may contain certain metabolites that could have proliferative activities on UL cells.

One notable finding of our study was that the association between dietary pattern and UL differed according to menopausal status. Several studies have reported differential dietary impacts on hormone-related diseases depending on menopausal status. A study on the effect of a diabetes risk reduction diet on endometrial cancer found that inverse associations were observed only in postmenopausal women, not in premenopausal women. Another study investigated the association between urinary isoflavone and urinary estrogen levels after isoflavone intake and found that their positive correlation was recognized only in postmenopausal women. Metabolic efficacy decreases by 10% and lipid metabolism becomes dysregulated after menopause. There is cumulative epidemiologic and metabolomics evidence that the postmenopausal state can affect a certain set of metabolites with the same type of diet compared to the premenopausal state. The anti-proliferative effect of the diet could be more evident in the high estrogenic milieu of premenopausal women, while the stimulating effect of diet, such as estrogenic chemicals in fatty fish or processed meat, seems to be more prominent in the hypoeestrogenic state of postmenopausal women. Therefore, when exploring the association of dietary intake, menopausal status should be taken into account.

5. Conclusions

In our study of Korean women who underwent pelvic ultrasonography, we found that high intakes of fish and poultry, but low intake of dairy products, were associated with a higher prevalence of UL. Additionally, vegetable intake was inversely associated with the prevalence of UL in premenopausal women. These findings suggest that dietary interventions could be used as a preventive strategy for UL, particularly in premenopausal women who are most affected by this common and problematic gynecologic disease.

AUTHOR CONTRIBUTIONS

MJK, SK, SYY and YSK contributed to conceptualization, data interpretation and writing the article. JEL and JY contributed to the data analysis, and editing the article. MJK, SK, JJK, SYY and JHS contributed to writing the article and critical revision of the article. All authors agree with the final version for publication and agree to be accountable for the integrity of the data published.

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CONFLICT OF INTEREST STATEMENT
None declared. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

ETHICS APPROVAL

The Institutional Review Board of the Seoul National University Hospital approved the study (15 Apr 2015, H-1504-034-662).

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Q and T represent quartile and tertile, respectively. The black circles indicate the study specific odds ratios (ORs) and the horizontal lines indicate the 95% confidence intervals (CIs).

Supplementary data

Supplementary Table 1. Median values of the tertiles or quartiles of each dietary group in all, pre-, and postmenopausal women.

References


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